AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 109. JULY, 1937 No. 7

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Annual Subscription, $3.00 Foreign Postage, 25 Cents Extra
Single Numbers, 30 Cents. Back Numbers, 50 Cents

Entered as Second-Class Matter at the Post Office at Philadelphia, Pa., Under the Act of March 3, 1879

Acceptance for Mailing at Special Rate of Postage Provided for in Section 1103, Act of October 3, 1917. Authorized February 15, 1920

EDITORIAL

On these pages the editor offers his opinions, unshackled by advertising patrons and unrestrained by anything save a sense of the decent and the truthful the editor, alone, is responsible for their type, their tone and their tenor.

THIS COSMETIC DEMOCRACY

A CENSUS of cosmetics has recently appeared in the popular press. It strikes an all-time record for cosmetic consumption in America. According to this authority nearly two billion dollars was spent in 1935 in this alleged "improving on beauty."

"America Again Leads the World"; such was the questionable caption of the article that sought to evaluate this cosmetic splurge.

But we must remember that nowhere had the cosmetic urge a better start than in North America. Long before the lichens and weeds around the Plymouth rock were disturbed by the hob-nailed shoes of Christian vagabonds, a race roamed our land whose decorative instincts were most intimate and personal. For Lo the Poor Indian was rich in vanity long before the paleface came.

No damsel or dowager of old ever spent more time with her toilet than a Sioux or Crow getting ready for a trip to his sweetheart's tent, or to the hunt for man or beast. One is not surprised, then, that with such a fine start in the business of feathers and flooey and finery, the cosmetic urge should have found this continent such an easy place to progress.

Yet, cosmetically or costumically, compared to the modern flapper, from child of ten to mother of ten, the Indian braves were pikers, and the squaws were nothing at all.

Read these salubrious statistics. Read them, and weep,—when you remember that the share of the corner drug store in this immense volume of business is insignificant compared to that garnered by beauty parlors all over the land.

Four thousand miles of lipstick, enough to reach from Hollywood to Coney Island, are used each year by the women of America between the ages 15 and 75. The estimate is based conservatively on two lipsticks per annum per person.

Also our fair sex uses approximately 500,000,000 boxes of facepowder which allows slightly over a pound to each individual, and

some 240,000,000 rouge compacts, not including the liquid and paste rouges.

These statistics show that the average woman spends $90 a year on cosmetics and beauty culture, striking a medium between the practically extinct "just soap and water" advocates, and the constantly increasing number who make a practice of regular professional beauty treatments.

Of this $90, one-sixth is spent for face-powder and rouge; one-sixth for creams; one-sixth for perfumes, toilet water, talc and other toilet powders; one-sixth for dentifrices; one-sixth for hair tonics, shampoos, and—sh-h—hair dyes; and the remaining sixth for miscellaneous preparations and for treatments.

Research on the theatrical stage and in society in New York intimates that the bulk of that almost $2,000,000,000 of beauty buying is done by women who were born to bloom unsung and unnoticed by the world—a vast section of the feminine population whose moods and skins need to be softened by the gentle manipulation of expert fingers weighted with fragrant creams, and whose talent for chatty conversation finds an outlet and an audience in thick and tepid air that smells of soap and singed and drying hair.

France, the great civilizer of Europe, never had such hectic cosmetic days. In the light of these stupendous figures how insignificant seems the fact that Madame de Pompadour's household at Choisy managed to spend 500,000 livres (about $100,000) for perfume alone.

And as decadent Rome, effeminate and effulgent from over cosmeticizing, and over-perfuming, fell before the malodorous masculinity of barbarian hordes—so too did the empire of du Barry and Pompadour, Versailles and the lady-like Louises—crumble before the unlovely and perfumeless, though not odorless rabble, that maneuvered the French revolution.

Not indeed that we would draw morals and inferences from these recitals as we consider our own nation's cosmetic indulgence, for between our days and the days of Rome are no comparable conditions. Only the rich in Rome—and the favored few of the Court of France—could afford these inordinate luxuries. The perfumed eras of the Empire of the Fleur de Lys meant the plunging of the peasantry in interminable debt from constant and extortionate taxation. The balmy sweet-scented baths of Rome robbed the govern-

ing race of the vitality and virility wherewith that valiant city had extended its ramparts to every corner of the earth.

But not so with America—for our cosmetic frailties are diluted by spreading over so much territory, and so they incur no envy and accomplish, if sensibly handled, but little basic damage. With us even our vanities are those of a democracy, for rich and poor alike share commensurably in the pastimes and pleasures of this luxurious age.

And so, indulgently do we close this bit of writing with the pun that "women can't go wan forever"; and why should they?

IVOR GRIFFITH.

The Determination of Potassium as Potassium Silver Cobaltinitrite. A. M. Ismail and H. F. Harwood. *The Analyst, 62,* 443 (1937). A method for the determination of small quantities of potassium is described. The potassium is precipitated by sodium cobaltinitrite in the presence of silver nitrate. The precipitate is found to be of constant composition, but no simple formula can be ascribed to it. It isprobably a mixture in constant proportions of $KAg_2Co(NO_2)_6$ and $K_2AgCo(NO_2)_6$. Alternative methods for treating this precipitate have been investigated. In one case it is dissolved in nitric acid and the silver titrated with ammonium thiocyanate. In the other method the nitrite content is determined by a ceric sulfate titration. The titration of silver gave satisfactory results only with quantities of potassium exceeding 0.1 mg.; by determining the nitrite content of the precipitate it was possible to determine as little as 0.03 mg. of potassium with an accuracy of 1 per cent. The authors have investigated also the effect of the presence of other metal salts on the determination of potassium; they have applied their method to the analysis of soil solutions with considerable success. L. A. R.

ORIGINAL ARTICLES

EXPERIMENTAL DETERMINATION OF THE AMOUNT OF "BENZEDRINE" IN A THERAPEUTIC DOSE FROM "BENZEDRINE INHALER"

By Nathan A. Simpson, Ph.G., Ph.C. and Elsie Simon, B. A.

The Authors, in this highly informative and ingenious article, actually measure an "inhalation" and prove with satisfaction, that the "inhaler" is a safe enough, and a perfectly scientific instrument.

EVIDENCE continues to accumulate [1, 2] that "Benzedrine" (benzyl methyl carbinamine, S. K. F.) is of value and widely used in the treatment of rhinological infections in both children and adults. The drug is administered for this purpose in vapor form by means of "Benzedrine Inhaler" and clinical investigations [3, 4] have shown that on an average, two inhalations in each nostril once an hour produce sufficient and adequate shrinkage of the nasal mucosa in 93 per cent. of the cases.

However, up to this time no work has been done on the quantitative determination of the amount of "Benzedrine" obtained in one treatment with "Benzedrine Inhaler." Consequently it seemed of interest to attempt an experimental evaluation of this factor in order to determine the margin of safety of the Inhaler and the possibility of untoward reactions from overdosage.

Procedure

Although with an inhaler tube the relative depth of inhalation and hence the amount of "Benzedrine" obtained obviously varies considerably with the individual, it was felt that the accurate determination of the maximum, minimum and average dose obtained by a series of cases would yield values which would be significant. Accordingly twelve normals, eight males and four females, were selected for the test. Each was given a new "Benzedrine Inhaler" (a) which was connected to the experimental apparatus as shown in Figure 1. The test tube (b) was charged with 1 cc. of acid of such concentration that 1 cc. would neutralize 1 mg. of "Benzedrine" base, 1 cc. of water and

2 drops of methyl red indicator. The subject was requested to inhale through an empty inhaler shell (c) in the same manner as with an ordinary "Benzedrine Inhaler." By this method the "Benzedrine" vapor was drawn from the inhaler through the acid in the test tube.

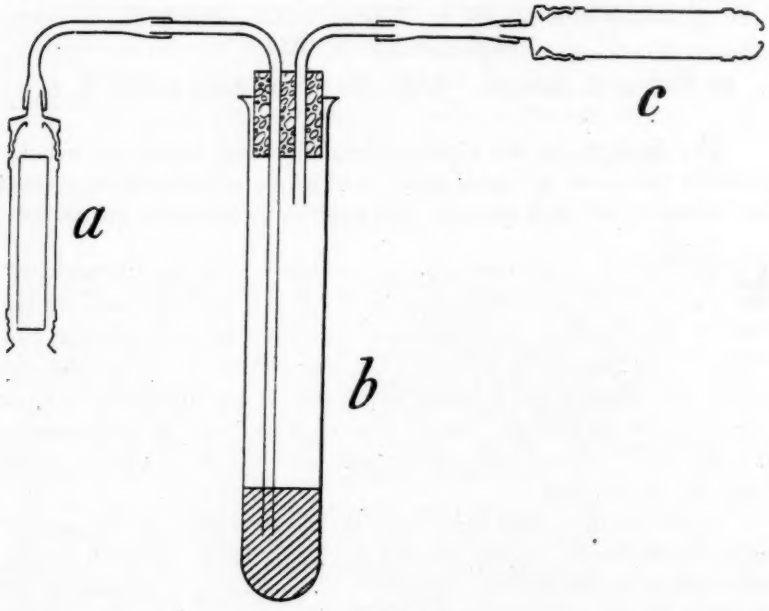


Figure 1

The subject continued to inhale in this manner until enough base was drawn into the test tube to neutralize the acid and change the indicator. The number of inhalations necessary to do this was recorded. In this manner the number of inhalations necessary to draw over 1 mg. of "Benzedrine" was determined. The test was repeated five times with each subject, 90 tests in all. The results are shown in Table I.

Results

This experiment indicates that on the average it is necessary to inhale 21 times in order to draw over 1 mg. of "Benzedrine" base, or an average of 0.048 mg. per inhalation. On this basis, in a therapeutic treatment of two inhalations in each nostril, four in all, the patient using the inhaler would theoretically receive an average dose of 0.2 mg. (Table II).

TABLE I

	Temp. ° C.	1st mg.	2nd mg.	3rd mg.	4th mg.	5th mg.	Average for 1 mg.
I (M)*	23°	22	25	25	24	16	22
	24°	18	17	18	18	19	18
II (M)	23°	20	17	18	11	18	17
III (F)	21°	13	13	21	14	15	15
	21°	23	29	25	30	22	26
	25°	14	17	19	19	21	18
IV (F)	24°	33	33	33	27	37	33
V (F)	24°	36	37	41	31	33	36
VI (M)	24°	20	17	23	24	17	20
VII (M)	24°	8	18	38	39	46	30
VIII (M)	25°	10	12	13	14	12	12
	24°	11	8	12	14	11	11
IX (F)	25°	6	12	13	13	11	11
	24°	17	20	22	16	19	19
X (M)	24°	27	35	42	42	40	37
XI (M)	25°	8	9	15	21	17	14
	25°	8	15	19	17	21	16
XII (M)	23°	22	35	25	12	17	22
Average		18	21	23	21	21	21

*M = male. F. = female.

The smallest number of inhalations in the whole series necessary to draw over 1 mg. of base was 6 and the largest 42. Hence the probable maximum amount per treatment (4 inhalations) obtained by actual use of the inhaler would be 0.67 mg. and the smallest 0.09 mg. However, due to natural loss through exhalation, the amount of "Benzedrine" absorbed systemically is undoubtedly considerably less than this.

Comments and Conclusions

In administering "Benzedrine" internally in the form of "Benzedrine Sulfate," the minimum lethal dose has been determined in rats as approximately 35 mg./kg.* With humans a single therapeutic dose has frequently been as high as 20 mg. and often considerably higher [5, 6]. In most cases 5 to 10 mg. is necessary in order to produce a noticeable effect.[7]

TABLE II

Average amount of Benzedrine (base) in:	Average	Low	High
1 inhalation	0.05 mg.	0.02 mg.	0.19 mg.
1 treatment—4 inhalations	0.20 mg.	0.09 mg.	0.67 mg.
1 day's therapy—12 treatments—[48] inhalations	2.40 mg.	1.06 mg.	8.04 mg.
Average number of inhalations necessary to obtain:			
1 mg. of "Benzedrine" base	21	6	42
15 mg. Benzedrine base (equivalent to 20 mg. "Benzedrine Sulfate"—an average oral therapeutic dose)	315	90	630

The figures in Table II show that it would be necessary to inhale approximately 315 times on the average and 90 times at least to obtain an amount of "Benzedrine" base equivalent to a 20 mg. oral, therapeutic dose. This is some 22 to 78 times the number of inhalations in a therapeutic treatment (4 inhalations) with "Benzedrine Inhaler" and some 2 to 6 times the number inhalations normally taken in a 24-hour period, allowing 12 treatments in that time. Moreover, these figures make no allowance for the obvious loss of "Benzedrine" through exhalation during treatment.** Thus the amount actually absorbed would be less and the margin of safety increased accordingly.

*35 mg./kg. of "Benzedrine Sulfate" is equivalent to about 26 mg./kg. of "Benzedrine" (benzyl methyl carbinamine) base as present in the inhaler.

**Determination of the loss of "Benzedrine" through exhalation will be the subject of a future study.

It may be concluded, therefore, that there is such an exceedingly wide margin of safety with "Benzedrine Inhaler," that serious toxic reactions are well nigh impossible unless there is flagrant overdosage or a definite idiosyncrasy is present. In the latter event, it would normally be manifest at the outset, and withdrawal of therapy would be indicated.

Summary

1. The average number of inhalations necessary to draw over 1 mg. of "Benzedrine" base from "Benzedrine Inhaler" has been determined experimentally to be 21, with a low of 6 and a high of 42.

2. The maximum amount of "Benzedrine" base theoretically obtained from a therapeutic treatment (4 inhalations) with the inhaler has been calculated to range between 0.67 mg. and 0.09 mg. with an average of 0.20 mg.

3. The amount of "Benzedrine" base theoretically obtained by 12 treatments (48 inhalations) with the inhaler (the average number during one day) averages 2.40 mg. with a high of 8.04 mg. and a low of 1.08 mg. This is approximately one-half to one-sixth of a *single* oral therapeutic dose.

4. Natural loss of "Benzedrine" through exhalation during treatment widens the margin of safety beyond that shown by the figures.

5. Due to an exceedingly wide margin of safety, serious toxic reactions resulting from the use of "Benzedrine Inhaler" appear unlikely, even with gross overusage.

Bibliography

1. Bertolet, J. A.: *Clin. Med. & Surg.*, 44: 25, 1937.
2. Scarano, J. A., and Coppolino, J. F.: *Arch. Pediat.*, 54: 97, 1937.
3. Sulman, L. D.: *Med. Times*, 63: 374, 1935.
4. Giordano, A. A. S.: *Penna. Med. Jour.*, 39: 20, 1935.
5. Peoples, S. A., and Guttmann, E.: *Lancet*, I: 1107, 1936.
6. Myerson, A., and Ritvo, M.: *J. A. M. A.*, 107: 24, 1936.
7. Myerson, A.: *Arch. Neur. and Psych.*, 36: 816, 1936.

DO CHEMICALS OR GERMS CAUSE DISEASE?

By T. Swann Harding

Once upon a time disease was believed to be due to devils within, then, for a while, it was miasmas without. Today most everyone thinks of disease as germ engendered. The author asks us to consider the role of chemicals as the causative factors of human and animal ills.

ALL men tend to become conditioned to the dominant truths of their own age. They would no more think of denying these truths than they would of confuting the axioms of Euclid's geometry. Many of them are so hallowed that they are regarded as quite self-evident and little effort is made by most people to validate them. Indeed there is something not quite decent about questioning them.

Thus if an ancient or modern witch doctor were asked the cause of disease he would assert that the ailing had been entered by evil spirits which must be exorcised before they could become well. If a traditional Chinese physician were asked the same question he would, however, start to speak learnedly of the Yang and the Yin principles and of the five elements, and would tell us that they were out of harmony in the ill, and must be reconciled.

Before Pasteur, illness was supposed to be caused by mysterious agencies that permeated us like noxious gases. But today most of us, if asked: What causes disease? would reply with the utmost certainty: Bugs, of course—having in mind the bacterial theory of disease causation associated with the names of Pasteur and Paul Muni. It might repay us to re-examine this so solemnly accepted truth in the light of some interesting recent discoveries.

I

First of all the theory itself greatly antedated Pasteur. He merely put it over, as the saying is. The idea that small particles of some sort, living or nonliving, cause disease is much older that we usually think. In discussing the cause of an Athenian plague that

occurred in 430 B. C. Lucretius wrote that: "Just as there are seeds of things helpful to our life, so, for sure, others fly about that cause disease and death." It will be remembered that Lucretius also formulated an atomic theory, so that it was rather easy for him to believe that some malignant little atoms caused disease.

Then there was the Roman scholar known as Varro (Marcus Terentius) who lived between 116 and 27 B. C., and who is said by some to have anticipated the modern theory of malaria's spread. For he wrote: "In building houses you must avoid the neighborhood of marshy places . . . because when the marshes begin to dry they engender a multitude of invisible insects which are introduced into the mouth and nostrils with the inhaled air and occasion serious illness."

There are those who would have us believe these "invisible insects" to have been bacteria. So perhaps they were, though this does not detract from the great work performed by Louis Pasteur. At the same time it is possible for us today to accept too blindly the theory of the bacterial causation of disease, and to apply it inappropriately. After all no scientific explanation is final. Each scientific truth is conditioned by certain limitations and each explanation is true only in so far as it fits snugly into the general pattern of science at that time.

The invariable finding of certain organisms in the case of certain diseases is not absolute proof that the organisms caused the disease. The association may be purely fortuitous and it has often been so proven. Thus a very definite germ was pointed out as the cause of hog cholera up until the time the late Dr. Marion Dorset of the Department of Agriculture showed this to be a virus disease fortuitously associated with the presence of the germs implicated. On the other hand we have increasing evidence that the presence or absence of nonliving and often inert chemical substances may itself cause disease, or, again, may occasionally render the individual plant, animal, or human being susceptible to germ infections.

Research reported quite recently would lead us still further in speculation. It has been shown both with respect to certain virus diseases of plants called mosaics, as well as with respect to tuberculosis, that certain nonliving chemical substances play a crucial if not the sole part in producing infection. Etiology and pathology tend more and more to slip away from the bacteriologist and into the sphere of the chemist. Oddly enough it was a chemist, Pasteur, who originally founded the science of bacteriology!

II

That certain chemicals will produce disease has long been known. Consider the poisons lead and arsenic and the variety of distressing symptoms they can produce, culminating fatally in many instances. The body itself has been shown in modern times to be a perambulating chemical factory and many of the chemicals it produces are deadly poisons. It controls the quantity of them within the organism, however, and thus finds them beneficial.

It is notorious that many cases of arsenic poisoning have gone to the grave unrecognized. The doctor mistook them for natural deaths from some infection or other and a murderer escaped justice. This has happened frequently in Great Britain where, unfortunately for the perpetrator of the deed, the body was at last dug up and the presence of arsenic demonstrated.

From Britain also came reports of that strange endemic disease called "Devonshire colic," long regarded as an act of God, or a disease of natural origin, caused doubtless by one of the many mysterious miasmas of the day. These miasmas were supposed to emanate from putrescent matter in swamps and to pervade the night air causing illness and death. But in the latter seventies a bright young British doctor found that the "colic" was lead poisoning induced by contaminated apple cider, whereupon he was ostracized by the community (and the local bartenders) as an enemy of the people.

Modern times have produced other poisons. In recent years numbers of people entered one of our great clinics suffering from what appeared to be jaundice of infectious origin. The puzzling thing was that so many cases should occur with a previous history of having treated rheumatism with certain proprietaries. Ultimately it turned out that these remedies contained a deadly drug called cinchophen which has a drastic action on the liver and ultimately produces illness and death simulating that from infectious jaundice.

Other patients went to their doctors in great distress, some of them completely prostrated by devastating illness and many of them having lost every single hair on their bodies. They had agonizing pains, suffered terribly and often died. This too was puzzling until it became apparent that they had been freely using a depilatory cream for excess hair removal which cream contained the deadly rat poison thallium acetate. Yet the directions said use as freely as you would ordinary pure cold cream!

We carelessly and repeatedly use many drugs today that were unknown to our forebears or were little known when they lived. Such drugs can produce a variety of ailments, ranging from skin disturbances that resemble infections to acute agony and actual death. Phenolphthalein, used in many laxative preparations, produces conditions resembling both infective skin rashes and infective kidney troubles. Aniline dyes in certain preparations for the hair cause skin eruptions or, in those still more susceptible, dreadful pains and prostration.

Aminopyrine (formerly known as amidopyrine, or pyramidon) poisons the bone marrow, where some of the blood cells are formed. It causes a disease called agranulopenia, with crises of fever closely resembling malaria in aspect. Metallic dyes for the hair produce a wide variety of symptoms that might superficially be attributed to bacteria. The drug ergot often produces a condition not infrequently mistaken for erysipelas.

Within the past two or three years a new and violent drug has come into common use as an obesity remedy. Though doctors warned against it laymen grabbed for it as it appeared in a variety of proprietaries. It is known as dinitrophenol. It takes over part of the job of the thyroid gland, but tragically botches it. The generation of body heat is enormously accelerated. The temperature may actually rise to 115 degrees before the organism literally burns itself out and death results from heat rigor, *i. e.,* the tissues are coddled like egg white.

Even in such well-known diseases as diphtheria and botulism it is not the infective agents or the germs themselves that cause the patient's distress. Instead it is the toxins or poisons secreted by the germs that render the patient ill and menace his life. The presence of the organism is a necessary adjunct to the appearance of the disease, but certain nonliving substances generated by the germs do the actual damage.

III

On the other hand small quantities of certain chemicals are vitally necessary to the body if we are to maintain our health. Within the last few years research work on vitamins, hormones, and certain mineral substances, has made these necessities known to all of us. The body simply must have minute quantities of thyroxin, adrenalin, and insulin, for instance, or health cannot be preserved and functions cannot be performed.

On the other hand, since all of these substances are powerful, slight excesses of them easily poison us. The same thing is true of hormones, vitamins, and minerals. Evidence accumulates that the over-abundant use of vitamins can cause alarming symptoms, while it is well known that insulin, thyroxin, and adrenalin must be used with extreme care or convulsions and death rapidly ensue.

Medical and nutrition research have demonstrated in recent years that many diseases long supposed due to the so-called natural causes producing disease in general were really due to a lack of certain essential elements in the organism. Hence they are called deficiency diseases and the process of making up for the lack becomes substitution therapy.

The medical use of insulin does not cure diabetes. It simply substitutes from outside the body the necessary quantity of a chemical substance usually manufactured by the body itself and absolutely necessary to its maintenance. The use of ovarian substance, thyroid substance, adrenalin, and pituitary extracts in medicine are other examples of substitution therapy, of giving the body chemicals it is either altogether unable to manufacture or else cannot produce in sufficient quantity for certain emergencies.

The body must likewise have definite quantities daily of calcium, phophorus, iron, and eight or ten other minerals. These it cannot manufacture. They must come from outside. It can, however, separate the particular element it needs from a chemical compound and discard the rest. Thus calcium is as readily assimilated from crushed limestone or precipitated chalk as from vegetable sources. In its absence certain bone diseases occur just as anemia follows iron deficiency.

When we come to the vitamins we again supply the body with chemicals it needs for, as they are isolated and crystallized, the vitamins prove to be white powders of definite chemical composition. Vitamin A is a carotene; vitamin C is cevitamic or ascorbic acid, and vitamin D is a sterol or fat now called calciferol. All of them contain carbon, hydrogen, and oxygen. The body must have them to prevent a variety of diseases such as ophthalmia, scurvy, beri beri, and rickets.

A glance at the past history of medicine shows that all these diseases were once regarded as infections. Serious efforts were made to discover the particular germ responsible for them. This was especially true of the disease pellagra. When Goldberger of the Public Health

Service began to attribute pellagra to a dietary deficiency (first supposed to be a lack of vitamin G, but now thought to be something else) partisans of the bacterial theory of its origin rose in arms against him. One noted doctor was sure he had identified the germ causing the disease.

IV

So there has really long been a tug of war between the bacteriologists and the chemists as to the origin of many diseases. Not long ago we were assured that the "bacterium" causing the disturbing effects of poison ivy had been found. Today this is discredited. Very recent scientific work inclines us more and more to the opinion that the absence of excess of minute quantities of certain chemical substances produce many diseases once attributed to germs. This does not refute the germ theory of disease, however. It refines and extends it.

There is, for instance, a devastating disease that wipes game ducks out by hundreds of thousands and is called Western duck sickness. For a long time its cause was unknown. Some attributed it to marsh gas or methane, others to hydrogen sulphide (of blessed sophomore memory), others still to unidentified poisonous salts in the water, to bad food, to a deficient diet, to parasites and, naturally, to bacteria.

Quite a number of germs were apprehended, haled into the court of the laboratory, charged with causing the disease, and dismissed for lack of evidence. Yet one microorganism did seem to be implicated however indirectly. That one was *Clostridium botulism,* Type C, a rare and unusual strain of the organism causing botulism poisoning, though not the kind affecting human beings. This bug did its work indirectly, producing toxins that knocked the ducks out.

Just the right temperatures combined with precisely the right salt concentrations in inland waters favored the reproduction of the germs and the increase of the poisons. The ducks drank the contaminated water, grew sick, and died—or so matters stood until some time last week. Then another scientist wrote a paper insisting that Western duck sickness was nothing more nor less than a form of selenium poisoning, so the question seems wide open again. This time a chemical and not a living germ at all is implicated.

The case of the disease called "milk sick" is somewhat similar. This was a violent plague a generation or so ago and literally

ravaged the country in certain sections. The common mortality from it was as high as fifty per cent. at times and Abraham Lincoln's mother was numbered among its victims. The disease existed in this country as far back as 1776, but was first described in print by Dr. Daniel Drake about 1810.

The disease had a variety of names, it was attributed to a startling number of varied causes, and was often mistaken for other and better-known diseases. Some blamed toxic emanations from the soil or the mysterious poison gases (miasmas) that arose by night, settled on grasses and vegetation and later poisoned both cattle and men. Others ascribed the disease to fungi or to mushrooms, to poison ivy or to certain poisonous salts the plants drew from certain soils.

Gradually, however, it was observed that human beings tended to fall ill of milk sick about the same time that cattle were suffering an epidemic of "trembles." The two came to be associated. Soon it was discovered that eating white snakeroot gave cattle their violent trembles and that the disease was transmitted to human beings in cow's milk. Then a germ was found on white snakeroot, it was examined closely, its personal habits were investigated, its portrait was drawn and it was called *Bacillus lactimorbi* and nominated as the cause of milk sick.

But that was wrong. For if white snakeroot plants were thoroughly dried and sterilized, they could still cause milk sick. Yet any living bacterium would be bound to die in the sterilization process. Finally, Dr. James F. Couch, of the Bureau of Animal Industry, isolated a white, crystalline compound from white snakeroot, as well as from two other plants that caused trembles and milk sick. He discovered its composition, reproduced the disease by using it in pure form, named it tremetol, and the problem was solved—a chemical, not a bug, being guilty.

Generally speaking if a germ is at fault the better nourished the body the less susceptible the individual is to infection. For a long time vitamin A, originally called the "growth" vitamin, grew slowly to be regarded also as an "anti-infective" vitamin. Specifically it was neither. Vitamin A does promote growth in the same sense that vitamins B, C and D, not to mention calcium and pituitary extract promote it, that is the process of growth is disturbed in their absence.

The absence of any element from the diet that is essential to the body also tends to increase susceptibility to infection. What is more

vitamin A does quite definitely prevent the eye trouble called xerophthalmia. But it is an aid in establishing the resistance of the body to infections only when the bodily reserves of vitamin A are exhausted and the intake is inadequate. It has not been shown specifically to prevent any sort of infection nor can the use of vitamin A in excess serve any such purpose.

Vitamin C, which as we have said is called ascorbic acid, gets its name from its effectiveness in curing scurvy, a disease characterized by hemorrhages from the mucous membranes, skin, and joints, and by trouble with the bone marrow, bleeding and spongy gums, easy bone fracture and painful or swollen joints. Oddly enough a somewhat similar set of symptoms appears in diphtheria; the symptoms are not exactly the same, but diphtheria toxin causes many of them.

What is even more curious, work on animals indicates that vitamin C enables guinea pigs to resist diphtheria toxin, small doses just sufficient to prevent scurvy being effective. Vitamin C would also inactivate diphtheria toxin if added to it in glass. Animals given liberal amounts of C were highly resistant to diphtheria. The old idea that foreign agents like bacteria cause disease is so firmly established that it is difficult for us to believe a dietary deficiency also produces susceptibility to diseases like diphtheria.

V

It begins to appear that bacteria alone do not cause many diseases once attributed to them; the absence or presence of certain chemical substances is also an essential. Possibly this does not mean that pathology will become wholly chemical in lieu of wholly bacteriological, but that both chemical and bacteriological agents conspire to produce many diseases formerly attributed to the latter acting alone. Possibly also this offers some explanation of immunity, the body chemistry of those who do not "take" an infection being such as to protect them.

It was but a generation ago that phytopathologists or experts in plant disease discovered that plants could have infections as well as animals or human beings. Both fungi and bacteria infested plants and the susceptible individuals became diseased. At once there followed a tendency to attribute every sort of plant disease to living organisms. At about the same time it was found possible to breed strains of plants of economic value that were resistant to the diseases and thus to protect our food and fruit supply.

More recently still, however, it has been found that many plant diseases charged up to germs are actually caused by deficiencies of such elements as iron, manganese, magnesium, boron, sulphur, copper, or zinc in the soil, all of which plants must have to thrive. A wide variety of vegetables and fruits fall ill when they do not get their minerals and the symptoms closely resemble those of an infectious ailment. Spots form, leaf areas die or become necrotic, leaves wilt or collapse, yellowing, mottling, or death occur.

In other instances the mineral lack simply renders the plant susceptible to the attack of some fungus or bacterium. Does the same thing occur with human beings? It begins to look so. Not long ago Prof. R. J. Anderson, of Yale, reported that he had grown more than two thousand quarts of tuberculosis germs and had isolated from them a hundred and seventy chemicals, with more to follow. One of these is a red coloring matter; another is the rare sugar, arabinose; another boasts the mysterious name phthioic acid.

The interesting thing is that an acid, a protein, and a sugar isolated from the tuberculosis germs can, when administered to the body separately, produce the lesions, the elevated temperature, and the other toxic conditions known as tuberculosis. However, the body quickly overcomes the effects of these chemicals unless it be infested with the tubercle bacillus. Then it cannot fight them off and the poisons overcome it. Hence two ways of curing tuberculosis seem possible: neutralize the nonliving chemical poisons, or asphyxiate the germs.

More and more it appears that living and nonliving agents combine to produce diseases. Sometimes one appears to predominate, sometimes the other. Neither can any longer be cited as the sole cause of disease. But is there not a dividing line between them? At just what point does nonlife end and life begin? According to the seemingly epoch-making work of Dr. W. M. Stanley, of the Rockefeller Institute for Medical Research, life appears to begin in the region of the ultrafiltrable virus.

VI

We must step back a little to see what Stanley has done. The mosaic diseases, so called because they produce pale-spotting or mottling of the foliage, are very common among plants. They are today regarded as virus diseases and are supposed to be transmitted

through seed, tubers, and cuttings, or by means of insect carriers. The diseases are important because they ruin many plants of economic value.

At one time these diseases were attributed to faulty fertilization or to microorganisms. One of the germs supposedly implicated was *Micrococcus toxicatus* Burrill. It also was drawn from life, described in detail, its shape and size were measured with care and recorded with diligence. It was shown to occur in chains and its vital movements were observed. All this was very well, but it never existed!

For further investigation proved that no such germ caused the mosaic diseases. They were next attributed to the malign effects of those tiny infective particles that slip through the finest of all laboratory filters. Promptly, of course, some investigators went too far and used this to explain everything. Thus two strawberry diseases were hastily charged up to a virus though they have since been found to be caused by worms, or nematodes, in one case and by inherited genetic variations in the other.

In many cases germs have been accused of causing certain animal and human diseases merely because they were usually found present in cases of the disease. Yet the real culprits, as was shown in hog cholera, smallpox, infantile paralysis, encephalitis and, possibly, influenza and the common cold, were none other than these extremely minute ultrafiltrable viruses. A wide variety of human, animal, and plant diseases are now supposed to have this same cause.

The virus is exceedingly potent. Water dilutions of one part virus to ten thousand or even to one hundred thousand parts are effective. Such dilutions have been much studied in the case of the mosaic which often ruins the better part of the tobacco crop in some regions. There are also mosaic or virus diseases that make life hard for potato and tomato plants.

The virus particles are far too small to be seen under any microscope. Estimates are that the figure ten followed by fourteen ciphers would approximately represent the number of such infective atoms in only twenty drops of juice squeezed out of a tobacco plant affected with mosaic. This estimate was made by using as a guide the size of the holes in the filter through which the virus slipped. But just what is the virus? It was long supposed to be a sort of midget germ that tagged along after the bigger, full-sized germs.

More than thirty years ago Dr. A. F. Woods, now Director of the Graduate School of the Department of Agriculture, suggested that diseases like tobacco mosaic were not caused by living organisms, but much more likely by enzymes or ferments. In 1932 it was announced from the Boyce Thompson Institute for Plant Research at Yonkers that a certain protein, a colloid, was the infective agent.

If true this is of tremendous importance. It would mark one of the greatest advances in medicine since the work of Pasteur, Lister, and Koch. It would throw doubt upon the idea that such diseases as smallpox and infantile paralysis are of microbic origin.. Possibly we should blame a crystalline chemical substance, a protein, for Stanley has isolated the protein that he regards as causing tobacco mosaic. In 1935 he prepared it from diseased tobacco plants, using about five tons of fresh tobacco leaves to make a third of an ounce of virus.

Later his technique improved and he got ten pounds of crystals from five tons of the leaves. Later still he prepared the same identical protein from tomato plants affected with tomato mosaic and concluded that this one chemical substance was the cause of both diseases in widely differing plants. He produced mosaic disease in healthy plants, using these crystals which, he reported, were not alive, yet were self-propagating. He called this an "autocatalytic protein." Though nonliving it possessed the attribute of reproducing itself when placed on favoring tissues.

According to a report by Dr. E. W. Brandes, of the Department of Agriculture, some plants possess the power of elaborating other chemicals that counteract the effect of the agents causing mosaic. He has produced from the tips of sugarcane stalks a chemical, which when injected into healthy sugarcane plants, will prevent them from contracting mosaic. This looks like a clear case of chemical combatting chemical.

VII

What of the future? The idea that a virus could be a chemical and could produce disease though not endowed with life has been under attack by the bacteriologists for some time now. Yet Dr. Donald D. Van Slyke, of the Rockefeller Institute, and its chief research chemist, declares that these findings of Stanley are a landmark in the history of the scientific attempt to solve the baffling problem of the virus diseases.

When Pasteur first discovered that germs could cause disease he was confident that he could, within a short time, produce an antitoxin for every known ailment. He failed to do this. So far it could be held that there were microorganisms too small to be seen, hence they could not be fought intelligently. But now proteins are discovered which lie half way between life and nonlife, and bacteriologists cannot argue their existence away.

Somewhere along the line between life and death there are chemicals, existing in a sort of middle ground, neither living nor nonliving, possessing some of the attributes of living organisms without themselves being alive. In view of this bacteriologists may be called upon to cede priority to chemists in seeking the cause of disease.

These proteins (proteins are usually known to us in the form of such substances as lean beef or white of egg) can, when applied to tissues they like, multiply. They can undergo mutations, or changes. They can produce diseases. Apparently the two known forms of tobacco mosaic are caused by slightly different proteins which so far can be differentiated only by the results they produce in inoculated plants.

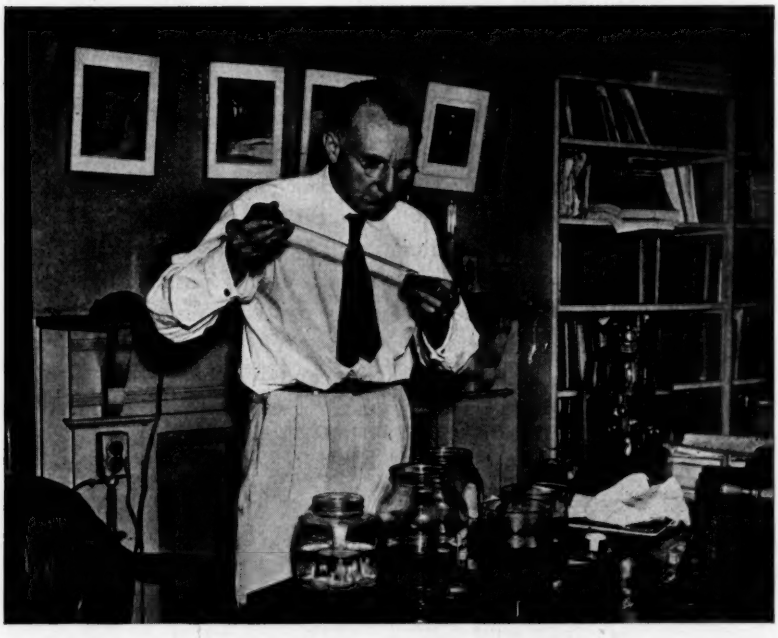
The old air-tight classifications of science appear to vanish before our eyes. The living and the nonliving, the chemical and the bacteriological become inextricably mingled. Progress will be impeded, however, if scientists permit argument about conventional classifications to disturb them. Cooperative effort is needed on the part of experts trained in several different sciences. Whether disease is mainly chemical or bacteriological in causation and whether living or nonliving agents produce infection, medical research must march on to victory.

THE DEVELOPMENT OF DAPHNIA MAGNA FOR THE EVALUATION OF ACTIVE SUBSTANCES

By Arno Viehoever*

Here is the story of Daphnia, the diminutive drug detective, told from its very beginning up to now, by Dr. Arno Viehoever, whose indefatigable research with this little creature, has accomplished unbelievable results, and promises even more.

AS the result of years of extensive investigation, the significance of Daphnia magna—as the biological or living reagent (1-3)—has been established in both scientific circles and in the public press.**



TheAuthor in his Laboratory **Courtesy Evening Bulletin**

*Director of the Laboratory for Biological and Biochemical Research (supported by Mr. William H. Gross, Philadelphia College of Pharmacy and Science).

**Time Weekly News Magazine, Vol. 29, No. 26, pp. 30, 32, 1937; The Merck Report, Vol. 46, No. 3, p. 17, 1937; Associated and Daily Press, June 21 and 22, 1937.

The essential features of transparency and ease of observation with the proper optics, and the abundance of standardized individuals for quantitative experiments permit the study of the mechanism and evaluation of drug action, therapeutic or toxicological. By standardization is meant uniformity in respect to age, genetics, sex, nutritional and environmental histories.

At present, co-operative daphnia research—with the assistance of the writer and his staff—is being conducted on cathartic and toxic substances at the College of Medicine of the University of Illinois and at the School of Pharmacy of Temple University, Philadelphia; on protective nutrition in co-operation with Dr. C. F. Church at the Children's Hospital of Philadelphia; on poison tests at the control laboratory of the U. S. Biological Survey by Mr. J. C. Ward and co-workers; in state and federal government laboratories in connection with insect control and water testing; by the American Association of Official Agricultural Chemists in connection with drug work; and, finally, at this laboratory for the United States Sugar Corporation in connection with development work.

In view of the increasing use of daphnia the author has been requested to summarize in a brief historical sketch the experimental ground work. He takes this welcome opportunity to acknowledge the assistance of his students or associates who have contributed to the evidence accumulated during more than ten years of often arduous, yet ever fascinating labor.

The use of the transparent, freshwater crustacean, daphnia, taxonomically grouped with the lobsters and crabs, is directly related to the symposium at the International Plant Congress in Cornell, N. Y. (1926) on digitalis, the heart tonic. During his participation in the discussion, the author questioned the validity of claims for achieved physiological standardization. He emphasized the inherent difficulties confronting the workers trying to standardize digitalis by the use of fatally toxic, though specific, tests on the hearts of various vertebrates. Moreover, he expressed the doubt that the suggested use of the degree of the toxic influence of digitalis preparations on the growth of plant seedlings would present a solution for standardization, since the effects would be unspecific and unrelated to actual therapeutic needs.

The author was subsequently amazed when he learned, confidentially, that his remarks had been resented by some as being

polemical. This incident made him realize the importance, if not the necessity, of finding a more suitable test animal. He assumed that a transparent or translucent animal would be the ideal living test object. Such an animal, he felt, would likely show the specific therapeutic and, if necessary, the toxic effects of digitalis preparations on the heart, normal or depressed. A search was then initiated to discover such an animal and to determine the suitability for the solution of the digitalis problem as well as other pharmacological and toxicological problems. (4-5.)

After a thorough literature survey and extensive inquiries among friends and colleagues his attention was focussed on the invertebrates rather than the vertebrates, especially on rotifers and crustaceans. Thus Dr. Philip P. Calvert, Professor of Invertebrate Zoology at the University of Pennsylvania, (questioned at length at a scientific gathering in the fall of 1926, of the Sigma Xi Honorary Fraternity), encouraged him to try members of Cladocera for his purpose. By the process of trial, error and elimination, Daphnia magna, the largest species, was finally selected as the most promising. However, years of work were required before the laboratory breeding of pure strains for experimental purposes was accomplished. Several more years of continued application were necessary before special optical apparatus and methods were perfected for observing the daphnia in order to conduct, first, preliminary and exploratory tests, and, finally, qualitative and especially quantitative experiments, so essential to standardization.

Encouraged by the interest of his friend Thomas S. Githens (M. D.), pharmacologist, and other scientists of the Mulford Biological Laboratories, the effects of various other drugs, such as digitol, alcohol and other preparations, were demonstrated there (as part of some co-operative work on digitalis carried out in 1926 and 1927), and here in the college to Drs. Horatio C. Wood, Marin S. Dunn, and students. From the start the possibilities with daphnia of studying the mechanism of life were discussed in the biological laboratory, and the potentiality of elucidating the mechanism of drug action and the standardization of drugs were also discussed in the Pharmacognosy Laboratory. With interest thus aroused and sustained, throughout his activity as director of the laboratories, help was obtained from students, graduates, undergraduates and assistants of whom he especially recalls the following: Mr. Joseph F. McDonnell,

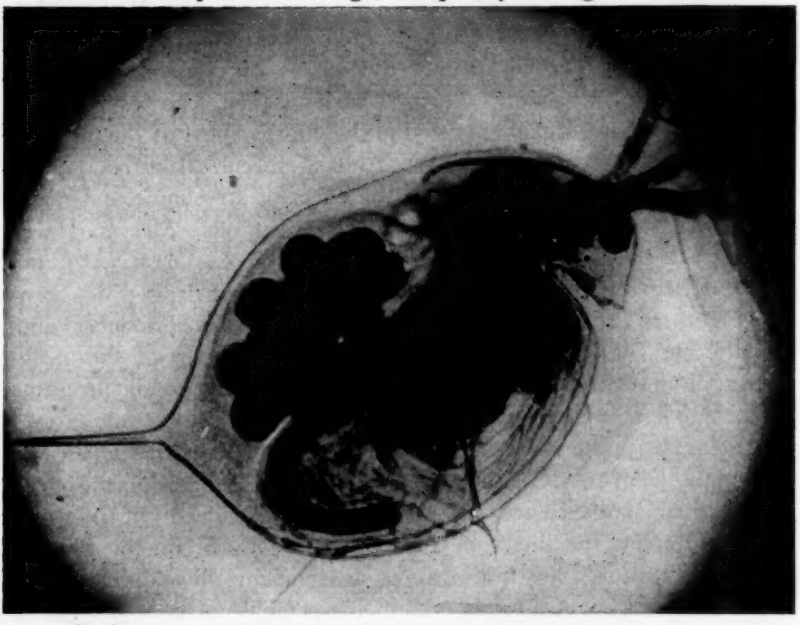
Jr. (6), as the first; worked with the small Daphnia (pulex?) obtained, upon the suggestion of the writer, or his former assistant, Dr. Dunn, from Dr. Calvert and fish food stores, while Messrs. Lewis G. Freeman (7), Manual Tubis (8), Edmund H. Maclaughlin, Bernhard Melkon, Ellen Cawley, and others worked with Daphnia magna in observing mainly the effects of digitalis and preparations. Messrs. Samuel Levin, Charles Cohen, Charles Skerrett, Jr., and Bernhard Melkon assisted in the improvement of the methods of recording and mounting; Mrs. Anna Schwenk Mikuriya (9-11) joined the author in the study of the effect of strychnine and many other drugs, depressants and digitalis preparations; Messrs. Harry Mack (12-13), Arnold B. Koff (14), Alfred L. Glass (15) and Charles Skerrett, Jr. worked on laxatives and other drugs; Mr. Samuel Kutner (16) did preliminary work on sex hormones; and, finally, Dr. Isadore Cohen (17) assisted in the survey of the mechanism of strychnine action and the attack of such important problems as vitamins, now in progress.

Until 1934 the work had been intermittently supported financially by grants from the Kilmer Research Fund, the Philadelphia College of Pharmacy and Science, the A. Ph. A., the Standard Oil Company of New Jersey, the Board of Trustees of the U. S. P., the Phenolphthalein Research Institute, Merck & Company, in addition to the writer's own personal funds. With the establishment in the fall of 1934 of the Gross Laboratory for Research, made possible by the initiative of Dean LaWall, the generosity of Mr. William H. Gross, and the whole-hearted support of the Board of Trustees, of the College, a steady progress was assured.

This progress has, upon invitation, been demonstrated in numerous lectures in various parts of the country, before professional, medical, chemical and pharmaceutical groups, scientific societies and naturalists, before executives and research staffs of leading manufacturing concerns, of various state governments and of the federal government. The numerous contributions, and the demonstrations of the author before the A. O. A. C. were sufficiently convincing to the governing board to lead to his appointment as the Referee on Daphnia Methods for the A. O. A. C.

In these efforts he has tried to show that daphnia responded not only qualitatively and quantitatively (in its heartbeat) to either small, non-toxic, or excessive, fatal doses of digitalis, but that it could in-

deed serve as a general biological reagent. (1-30.) Its establishment as such a reagent was not merely a happy stroke of chance, but the result of an unspoken challenge, accepted years ago.



Daphnia—

Diminutive Drug Detective

Left: Brood sac with many embryos; above heart chamber
Center: Food canal; above swimming organs and eye
Right: Breathing organs; above nephridia

While the largest species, Daphnia magna, reaches only one tenth of an inch, its transparency permits magnification to clear images of the size of man and beyond. In spite of its amazing simplicity of organs, these respond very similarly to our own. The principal systems: muscular, (circulatory, respiratory and digestive); nervous, (optic); and glandular, (reproductive) units function before our eyes, so that we can follow the very mechanism of life—the pulsating of the heart, the digestion of the food, and the response of tissues to medication or toxic influences.

This transparent living reagent, we are confident, fits well into the operative scope of the biochemist. His test tube (thus enlivened)

will furnish the experimental background for a century of important medical research and perhaps replace—as Dr. Mayo, the eminent surgeon from Rochester, Minn., hopes it will—the last century of the scalpel.

A new world for experimentation has thus been opened with the availability and abundant use of standardized daphnia. Our further aim is to utilize this organism in an ever-widening scope in the role of the biological reagent. The results obtained with it, we trust, will continue to serve as a welcome guide in experiments with more common experimental animals and in clinical therapeutic studies with man, and thus assist in the better understanding of life and the preservation or restoration of health.

REFERENCES AND RECORDS

(1) Viehoever, Arno: Daphnia—The Biological Reagent. *J. A. Pharm. Assoc.*, 25, 112-117, 1936.

(2) Viehoever, Arno: Daphnia, as a Biological Test Animal. *A. J. Pharm.*, Vol. 109, No. 2, 1937.

(3) Viehoever, Arno: Cardinal Points in Favor of Daphnia. *A. J. Pharm.*, 109, No. 5, 260-262, 1937.

(4) Viehoever, Arno: Transparent Life. *Am. J. Pharm.*, 103, 252-278, 1931.

(5) Viehoever, Arno: The Heart. *A. J. Pharm.*, 100, 718-745, 1928.

(6) McDonnell, J. F.: Low Animals as Test Objects in Drug Evaluation. M. Sc. Thesis, 1927.

(7) Freeman, Lewis G.: A Digitalis Preparation for Intravenous Injection. *A. J. Pharm.*, 463-473, 1928 (B. Sc. Pharm. Thesis, 1928).

(8) Viehoever, Arno, and Tubis, Manuel: Effect of Digitonin on the Heart of Daphnia. *J. A. Pharm. Assn.*, 18, 1137, 1929 (Kilmer Research).

(9) Viehoever, Arno, and Mikuriya, A. S.: Effect of Digitoxin on the Heart of Daphnia: *J. A. Pharm. Assn.*, 18, 1137, 1929 (Kilmer Research).

(10) Mikuriya, A. S.: The Effect of Drugs on the Heart of Daphnia. M. Sc. Pharmacog. Thesis, 1930.

(11) Viehoever, Arno, and Mikuriya, A. S.: Effect of Strychnine Upon Daphnia. *J. A. Pharm. Assn.*, 21, 239-242, 1932.

(12) Viehoever, Arno, and Mack, H.: Biochemistry of Amygdalin. *A. J. Pharm.*, 107, 397-450, Oct., 1935.

(13) Viehoever, Arno, and Mack, H.: Biochemistry of Podophyllum Peltatum I. *J. A. Pharm. Assn.* (in prep. for pub., M. Sc. Chem. Thesis).

(14) Koff, Arnold B.: Biochemistry of Podophyllum Peltatum II. B. Sc. Chem. Thesis, 1936.

(15) Glass, Alfred L.: Biochemistry of Podophyllum Peltatum II. B. Sc. Chem. Thesis, 1937.

(16) Kutner, Samuel: Daphnia as a Test Animal in the Diagnosis of Pregnancy. B. Sc. (Bact.) Thesis, 1937.

(17) Viehoever, Arno, and Cohen, Isadore: Mechanism of Strychnine Action I. The Physiological Evaluation. *A. J. Pharm.*, 109, 285-316, 1937.

(18) Viehoever, Arno: Daphnia—Life Mechanism. Micro Movies—1932.
(19) Viehoever, Arno: Yeast in Welfare and Industry. *A. J. Pharm.*, 105, 114-144, 1933.
(20) Viehoever, Arno: Report on Rhubarb and Rhaponticum. *J. Assn. O. A. Chem.*, 16, 530, 1933.
(21) Viehoever, Arno: Effect of Digitalis and Its Glucosides Upon the Chloroformed Heart. Micro Movies—1933.
(22) Viehoever, Arno: Water, Life, Blood. Popular Science Series, Vol. 11, pp. 178-202, 1934.
(23) Viehoever, Arno: Effect of Cascara on Daphnia. Micro Movies—1934.
(24) Viehoever, Arno: Effect of Pheno-Barbital on Strychnined Daphnia. Micro Movies—1934.
(25) Viehoever, Arno: Evaluation of Aloe. *A. J. Pharm.*, 107, 47-72, 1935.
(26) Viehoever, Arno: Evaluation of Carthartic Drugs. Presented before N. Y. Pharm. Assoc., 1935.
(27) Viehoever, Arno: Daphnia Propagation for Experimental Use. *A. J. Pharm.*, 107, 103-130, 1935.
(28) Viehoever, Arno: Adding Color to Life. Presented before Penna. Acad. Science, 1936.
(29) Viehoever, Arno: Effective Antidotes. Presented before A. A. A. Sc., 1936.
(30) Viehoever, Arno: Physiological Characteristics of Rotenone. *J. Eng. & Ind. Chem.*—Unpubl.

The Thermal Decomposition of α-Tocopherol. E. Fernholz. *J. A. C. S., 59,* 1154 (1937). The substances isolated from wheat germ oil and later from cottonseed oil, having the biological properties of vitamine E, appear to be alcohols and are known as "tocopherols." Their empirical formula suggests they are isomers of $C_{29}H_{50}O_2$, in which one of the oxygen atoms is present in a hydroxyl group. When α-tocopherol is heated, decomposition sets in with the formation of a crystalline compound which was identified as durohydroquinone. This thermal degradation seems to be best explained by assigning to α-tocopherol the structure of a mono-ester of durohydroquinone. The ultra-violet spectrum of the isolated compound, its insolubility in alakalies, and its high reducing powers to methyl alcoholic silver nitrate, as well as lack of reducing properties in its esters are also in good agreement with such an assumption. W. G. B.

REVIEWS

RECENT REPORTS ON PRONTOSIL, SULFANILAMIDE, AND RELATED COMPOUNDS

By Louis Gershenfeld, P. D.; Ph. M.; B. Sc.

This splendid review of the recent literature of the new and widely heralded peer of antiseptics, Sulfanilamide, deserves a careful reading.

IN the January, 1937, issue of this JOURNAL, the writer considered Prontosil and Prontylin, both patented products, and reviewed the use of these preparations in streptococcic infections. In April of this year, the Council on Pharmacy and Chemistry of the American Medical Association presented a brief report of these and many similar preparations which, however, are not protected by patents (*J. A. M. A., 108,* 16, 1937): We find similar products marketed under the names: Colsulanyde, Rubiazol, Stramid, Streptocide, Streptozone, and Prontosil Album. At that time the Council voted to accept the name "Sulfanilamide" for para-aminobenzene-sulfonamide preparations. Definite benefit occurs when using these compounds in streptococcal, meningococcal, and other infections caused by cocci. Favorable results have been obtained in other infectious processes. Oral administration is preferred to other modes of administration. Several articles with abstracts concerning the use of these drugs follow.

In a recent report, the Council on Pharmacy and Chemistry issued findings on sulfanilamide and related compounds. Their conclusions are of interest.

Sulfanilamide and Related Compounds. Am. Med. Assoc., Council on Pharm. & Chem., *J. A. M. A., 108,* 22 (1937). The original Prontosil (hydrochloride of 4-sulfamido-2′ : 4′-diaminoazobenzene) is not considered. Although this is the original product investigated and found to be of therapeutic value, it is not being promoted because Prontosil Soluble and Sulfanilamide are considered to be superior products.

It seems doubtful whether the Winthrop Chemical Company is justified in using the name "Prontosil" for Prontosil Soluble (disodium salt of 4-sulfamido-phenyl-2′-azo-7-acetylamino-1′-hydroxy-naphthalene-3′ : 6′-disulfonic acid), since the name has already been used for the previously named compound. It may be granted that Prontosil Soluble (2.5 per cent. solution) has been shown to be therapeutically useful in many hemolytic streptococcus infections, but apparently it has no demonstrated advantage over Sulfanilamide except in the matter of stability in solution and availability in ampules. It is promoted for parenteral administration only. The advantage of greater solubility would seem to be discounted by the fact that a 2.5 per cent. solution is theoretically equivalent to a 0.73 per cent. solution of Sulfanilamide. However, at 37° C. it would be possible to prepare a more concentrated solution of Prontosil Soluble and at lower temperatures the 2.5 per cent. solution remains stable. Although in the therapeutic results reported it has generally been administered in less than this equivalent amount, it has not been shown by carefully controlled experiments that when given in less than equivalent amounts it is as effective as Sulfanilamide given in greater than equivalent amounts. Neither has it been shown that Prontosil Soluble, if given in amounts equivalent to the usual doses of Sulfanilamide, would not be more toxic than the latter. It has the disadvantage of coloring the tissues red.

Sulfanilamide (para-amino-benzene-sulfonamide) is apparently the active principle of the compounds just mentioned. It is colorless, relatively inexpensive and can be administered parenterally or orally. It has the apparent disadvantage of being relatively insoluble (0.8% at 37° C. and 0.4% at 15° C.) and, because of its tendency to crystallize out of solutions, has not been made available in prepared solution ready for injection. It is marketed in the form of tablets containing 0.3 gm. and 0.5 gm. of the drug mixed with an excipient and as Sulfanilamide powder. The tablets are not suitable for dissolving in solution for parenteral injection. For such purpose the Sulfanilamide powder should be used.

The Council voted to accept Sulfanilamide for inclusion in New and Nonofficial Remedies as a therapeutc agent for the treatment of infections by hemolytic streptococci of Lancefield's serologic group A. The Council will proceed with determining the acceptability of the various brands that have been submitted.

Prontosil "Steals the Show" at Major Medical Convention, Science News Letter, June 19, 1937. Prontosil, new chemical remedy that has already saved thousands of lives and promises to conquer four of mankind's major germ enemies, held the spotlight at the meeting of the American Medical Association at Atlantic City. This red dye and its chemical relative, sulfanilamide, were the most important and most talked-up of subjects on the program and around the convention hall.

The latest disease to go down before the attack of sulfanilamide is pyelitis, serious and troublesome urinary tract infection for which there has hitherto been no very successful treatment. Cases of pyelitis which were completely cleared up by treatment with sulfanilamide were reported by Dr. Henry F. Helmholz of the Mayo Clinic, Rochester, Minn. This was the first report of the use of the new chemical remedy for the disease. Dr. Helmholz was to have reported results of treatment with mandelic acid, but his results with sulfanilamide were so much better and so spectacular that he made a last-minute change in his paper in order to report the sulfanilamide treatment. Meningitis, including the particularly deadly variety due to streptococcus infection of the brain membranes, as well as pneumonia, gonorrhea, childbed fever, and other diseases caused by streptococcus infection, all yield to treatment with sulfanilamide or Prontosil.

Reports of hundreds of similar cases are now ready for publication in the Journal of the American Medical Association, the editor, Dr. Morris Fishbein, declared. The chemical is not an antiseptic and does not kill the disease germs. Its action apparently is to keep the germs from growing and multiplying in the patient's body. The body's own fighting forces are consequently able to overcome the infection, and the patient recovers.

Sulfanilamide is apparently particularly effective in checking the growth of the round germs of the great "coccus" family. These include streptococci, pneumococci, meningococci, and gonococci. These bacteria are the causes of type III pneumonia, for which there has been no such satisfactory serum treatment as there is in types II and I; streptococcal meningitis, which up to now has always been fatal; gonorrhea, for which there has never been the specific treatment that there is for syphilis; childbed fever, which has killed thousands of mothers every year in spite of all efforts to check it; and the dis-

tressing and painful disease erysipelas. All have now been successfully treated by sulfanilamide or Prontosil.

This new chemical remedy was developed by a German chemist, G. Domagk. It was first brought to the attention of physicians generally by the English doctors, Leonard Colebrooke and Meave Kenny. Its first use in the United States was by Drs. Perrin Long and Eleanor Bliss of the Johns Hopkins University. Drs. Bliss and Long told the meeting of precautions necessary in the use of the remedy.

"Sulfanilamide is not aspirin and should not be used for every Tom, Dick, and Harry of an infection," Dr. Long warned physicians attending the meeting. The wave of enthusiasm for this drug is leading to its indiscriminate use by physicians all over the country for infections with many organisms other than the hemolytic streptococci, meningococci, gonococci, and pneumococci. Commenting on this, Dr. Long said he was "terrified" at the probable result. It will not help diseases due to other organisms than those mentioned above and may produce toxic effects in the patients which will bring the remedy—so useful in some conditions—into general disrepute. Dr. Long reported that dizziness, nausea, rashes, acidosis, cyanosis, and acute hemolytic anemia have followed the use of the drug in some cases. It should only be used for proved cases of streptococci, meningococcal, and gonococcal infections and then, Dr. Long declared, only under the closest supervision of a physician.

Prontosil in the Treatment of Gangrene. Science-Supplement, July 2, 13, 1937. Gas gangrene, the most serious danger in war wounds, and frequently fatal, can be successfully treated with the new chemical remedy sulfanilamide, or Prontosil as it is also called. Case reports and laboratory studies showing this were reported by Drs. Perrin H. Long and Eleanor A. Bliss, of the Johns Hopkins Hospital and University, at the recent meeting in Ottawa of the Canadian Medical Association. The laboratory work was done by Drs. Long and Bliss and the patients were treated by Dr. Harold Bohlman, also of the Johns Hopkins Hospital.

Drs. Long and Bliss were the first to use the new chemical remedy in this country in cases of deadly hemolytic streptococcus infections. They and others have found that sulfanilamide is highly sucessful in treating infections of the streptococci and also infections of pneuomocci, meningococci and gonococci. The particular diseases for which the chemical has been used include scarlet fever, erysipelas,

chilblain fever, meningitis, type III pneumonia and gonorrhea. Gas gangrene is due to infection of the wounds with still another disease germ, generally referred to as the Welch bacillus. It occurs particularly in cases involving severe bruises of the deep tissues about the wound, especially if cloth or dirt has been carried into the wound. The disease gets its name gas gangrene from the fact the germ causes gas bubbles to form as it invades the tissues. Treatment of the condition has heretofore not been very successful and it often has been necessary to amputate an arm or leg to save the patient's life.

The Use of Sulfanilamide (Prontylin) in Urinary Infections. E. N. Cook and H. A. Buchtel; *Proceedings of the Staff Meetings of the Mayo Clinic, 12,* 24 (1937). In February, 1935, Domagk was the first to demonstrate the prophylactic action of azosulfonamide derivatives on hemolytic streptococci experimentally. Soon it was found the azo radical could be eliminated without impairing the bactericidal property of the drug. Many German investigators have carried on this work and have demonstrated definitely the value of this drug, but their earlier reports stated that the drug had a variable effect in sterilizing infected urine.

About six months ago sulfanilamide was first used at the Mayo Clinic in the Section on Urology. Because of conflicting reports and the suggested danger incident to its use, we proceeded very cautiously and used only small dosages. In this early series we noted little benefit from the drug when given orally to patients with infection of the urinary tract.

Our later results have been very encouraging. In more than 90 per cent. of the uncomplicated cases of bacilluria caused by Escherichia coli, Aerobacter aerogenes, Shigella, and so forth, the infection has been eradicated completely and the urine has been made negative. This was determined by repeated Gram's stains and on culture. Of interest has been the marked discrepancy in the recorded concentrations of prontylin in the urine. We have noted a distinct relationship between these various concentrations and the *p*H of the urine. In cases in which a relatively high value for prontylin was maintained in the urine, the acidity of the urine was greater than in cases in which the concentration of prontylin was low. In the latter the urine was alkaline.

The work of Marshall, Emerson and Cutting and also that of Fuller and others demonstrates two definite forms of sulfanilamide. Drs. Helmholz and Osterberg are reporting the same finding. Further studies are now being carried out to prove or disprove the relationship and importance of the concentration of these two forms and the value of the *p*H of the urine.

To date, the coccal infections for which we have used prontylin have not responded as well as the bacillary infections. However, it is too early to make a definite statement regarding this. Herrold, of Chicago, in a personal communication stated that with certain forms of staphylococcus he has had results which equal those obtained in bacillary infections and our recent experience tends to confirm this.

On reviewing the cases of urinary infection in which prontylin has been employed at the Clinic we have noted that in those which did not respond to prontylin therapy, the dosage was almost always inadequate. Because of conflicting reports concerning the dangers of this drug we gave at first only 5 grains (0.3 gm.) three times a day and little or no benefit was obtained in the cases in which it was used. Our later work has shown us the advisability of somewhat larger doses and our results have improved greatly. At present we recommend 30 grains (2 gm.) the first day, 40 grains (2.65 gm.) the second day, 60 grains (4 gm.) the third day, and 40 grains (2.65 gm.) each day thereafter.

Any untoward reaction should be noticed, and the dose should be reduced if the symptoms become at all alarming. Occasionally complete quiet or even rest in bed may be necessary to allow the taking of the drug. Tinnitus, headaches and dizziness are some of the unpleasant reactions. We shall leave the consideration of these for a more detailed report which Drs. Bannick, Brown and Habein will present later.

Apparently the development of a bactericidal urine following the administration of sulfanilamide is not as dependent on an adequate renal function as the development of a bactericidal urine following administration of either the ketogenic diet or mandelic acid. In two cases of long-standing infection of the urinary tract in which the values of urea in the blood were well over 100 mg. per 100 cc. we have been able to sterilize the urine. In one case both ureters were dilated grade 3 to 4. The other patient had been treated previ-

ously by administration of mandelic acid, and the problem of obtaining a satisfactory level of the urinary *p*H had been a baffling one. Under prontylin therapy the level of the urinary *p*H continued to be high, but this did not affect the formation of bactericidal urine. This apparent inconsistent relationship between the level of the *p*H and bactericidal urine has been noted throughout our entire series. If this fact continues to be true, this drug should prove of inestimable value in treating infections of the urinary tract caused by urea-splitting organisms, such as Proteus and various cocci, in which the urinary *p*H is high and it has been almost impossible to obtain a sufficient degree of acidity to permit the formation of a bactericidal urine after administration of the ketogenic diet or mandelic acid. Apparently such a *p*H is not necessary when using prontylin.

This preliminary report is presented to show the value of the sulfanilamide as an urinary antiseptic. The results obtained in a small clinical group are presented; an adequate dosage is recommended, and certain untoward reactions are mentioned. Dr. Buchtel has suggested the probability of this drug being excreted in the prostatic secretion, and our early tests confirm this. Further studies are being carried out along this and other lines, concerning use of sulfanilamide in infections of the urinary tract.

Rate of Excretion and Bactericidal Power of Sulfanilamide (Prontylin) in the Urine. H. F. Helmholz and A. E. Osterberg, *Proceedings of the Staff Meetings of the Mayo Clinic, 12,* 24 (1937). Pursuant to early investigations in Germany on the bactericidal activity of azo dye substances, it was determined that certain of these which contained a sulfamido group were markedly effective in the treatment of streptococcal sepsis of mice. It was demonstrated later that such substances had the same effect in human beings. The first of these compounds which was made about 1908 was sulfaminoazobenzol. This substance, however, lacked solubility and was not suitable for parenteral injection. Further research led to the synthesis of substances with sufficient solubility for parenteral injection and which, at the same time, had a bactericidal efficiency at least equal to that of sulfaminoazobenzol. The final result of this synthetic work was the development of prontosil, a sulfamidonaphthalene-sulfonic acid.

It was recognized that after administration of prontosil, para-amino-benzenesulfamide was excreted and it was postulated that

perhaps the bactericidal activity was due to this compound. This substance existed in the urine both in its free state and as an acetyl derivative. In dogs acetylation did not take place. This is an excellent example of another instance in which acetylation of compounds does not occur in the dog as in man.

Further work is now directed toward the therapeutic effects of para-aminobenzenesulfamide known as sulfanilamide or prontylin. The levels of sulfanilamide excreted in the urine by patients ingesting therapeutic doses of this drug reveal that approximately 100 mg. of free sulfanilamide per 100 cc. of urine and 90 mg. of conjugated sulfanilamide per 100 cc. are excreted on the third day when the daily intake of this drug is 30 grains (2 gm.) per day. Approximately 60 mg. of free sulfanilamide per 100 cc. of urine and 100 mg. of conjugated sulfanilamide are excreted at some period when the intake of this drug is 75 grains (5 gm.) for only one day.

The continued work on the bactericidal properties of the urine after the oral administration of sulfanilamide reveals that it has specific action on the bacteria which usually cause urinary infections. At one end of the bactericidal range is the staphylococcus which seems to be the organism which is most easily killed off and at the other end is the Streptococcus faecalis which grows luxuriantly in a urine that will kill off the gram-negative group of bacilli in twenty-four hours.

The urine after administration of sulfanilamide tends to be alkaline in reaction so that our early experiments were entirely with urine having a *p*H of more than 7.0. Urine containing 57 mg. of free and 68 mg. of conjugated sulfanilamide per 100 cc. had very much less bactericidal power than one containing considerably less sulfanilamide. The former had a *p*H of 6.0. There was a great increase in bactericidal power of this urine, when it was alkalinized from *p*H 6.0 to *p*H 7.5. Other experiments with urine from patients who were given sulfanilamide by mouth as well as when sulfanilamide was added directly to the urine, demonstrated that the drug was more effective in an alkaline urine.

A comparison of the bactericidal power of the free and conjugated forms of sulfanilamide as excreted in the urine and the free form when added to the urine seems to indicate that the conjugated form is the more potent. Further work at different levels of *p*H will have to be done to prove this to be constant. The inability to change the

strongly alkaline reaction of the urine in infections by Proteus ammoniae renders mandelic acid and the ketogenic diet almost useless in the treatment of these infections. It is of great interest to know that sulfanilamide had a very marked bactericidal effect on seven strains of the Proteus group. In an acid reaction, the bactericidal effect of the drug was almost absent. This emphasizes the effect of an acid reaction of the urine in reducing the bactericidal power in sulfanilamide.

In our clinical use of mandelic acid we have frequently been able to clear up urinary infections in from twenty-four to forty-eight hours. The same thing holds true for sulfanilamide. The administration of sulfanilamide does not offer the difficulties that the administration of mandelic acid does. For this reason sulfanilamide has an advantage over mandelic acid.

The question of dosage still needs a good deal of consideration but we can say that 5 grains (0.3 gm.) three to five times a day has been well tolerated by children from three to six years of age. Several children have continued to take the drug for a period of two weeks without harmful effect on the bone marrow, liver or kidney. Until we know more about the possible toxic action of the drug, patients taking sulfanilamide should be under careful supervision.

Summary and Conclusions.

1. Sulfanilamide given by mouth produces a urine strongly bactericidal for the organisms usually found in urinary infections with the exception of the Streptococcus faecalis.

2. The conjugated form of sulfanilamide seems to be more effective than the same concentration of the free form.

3. The same concentration of the drug is more bactericidal in alkaline urine than in acid urine.

4. Its ease of administration, its action in an alkaline urine, and its successful use in rapidly clearing up infections resistant to mandelic acid makes sulfanilamide a urinary antiseptic of great value. So far it has proved useless in infections of the urinary tract due to Streptococcus faecalis.

The Use of Sulfanilamide in Gonococcic Infections. Preliminary report. J. E. Dees and J. A. C. Colston, *J. A. M. A., 108,* 1855 (1937). The favorable reports of *p*-aminobenzenesulfonamide (sul-

fanilamide) upon meningococcal infections has suggested the investigation of its effect upon the closely related gonococcus. Forty-seven patients with various types of gonococcic infection of the genito-urinary tract were given this chemical. No other treatment was used, either local or general. In 75 per cent. of the cases the gonococci and the urethral discharge disappeared in less than five days. In five cases the subjective symptoms disappeared completely; there was a marked diminution in the amount of urethral discharge, but the gonococci were still present. In three cases there was no demonstrable response to the drug. In three cases there was prompt response, but as treatment was discontinued there was a recurrence of the infection; the infection disappeared in two of these cases following a second course of treatment. There was an absence of progression of infection, even in those cases which showed no response to treatment.

The Use of Sulfanilamide in the Treatment of Gonorrhea. Report of results in one hundred cases. F. A. Reuter, *Med. Ann. Dist. Columbia 6,* 117 (1937). Sulfanilamide produced clinical recovery from gonorrhea, in an average of five days, in 90 out of 100 cases treated. The drug was given in doses of 40 grains daily (10 grains after each meal and at bedtime). Cure was considered effected upon the disappearance of microscopic pus from the urine, absence of pus from the prostate gland, loss of all symptoms and failure to produce a recurrence. Such cures had been established for periods of two weeks to 4.5 months at the time of writing. The drug gives promise of being a most satisfactory treatment for gonorrhea. However, in view of the possible danger in toxic reactions, it should be dispensed only on prescription, and prescriptions should be refilled only upon the advice of the attending diagnostician.

Two Cases of Streptococcic Meningitis Treated Successfully With Sulfanilamide and Prontosil. Max H. Weinberg; Ralph R. Mellon and Laurence E. Shinn. *J. A. M. A., 108,* 1948 (1937). Two patients seriously ill with streptococcal meningitis, one of them of the highest severity, were treated successfully with the combined use of sulfanilamide and Prontosil. One patient recovered fully in a little more than two weeks, while the other still had partial paralysis of the third nerve at the time of writing. Streptococcic meningitis was regarded as practically hopeless. In view of this and the authors'

clinical experience with these drugs, they urge that they be used promptly in all cases. Oral, rectal (when the patient could not swallow), and intramuscular injections were used. The authors believe that intraspinal therapy should be used only as a last resort.

The Use of Prontosil in the Treatment of Erysipelas. W. H. Park, *Preventive Med. 7,* 40 (1937). The use of antistreptococcic serum in the form of antiscarlatinal serum in erysipelas is being supplanted by use of intramuscular injections of Prontosil and the oral administration of Prontylin. The results are most satisfactory.

Erysipelas Treated by Prontosil. R. H. Blair, *Brit. Med. J. I,* 836 (1937).

Treatment of Erysipelas by Prontosil. J. E. Minkenhof, *Nederl. Tindschr. Geneesk. 80,* 5197 (1936); through *Dermatol. Wochschr. 104,* 556 (1937). Of 35 cases of erysipelas treated orally with Prontosil, only one died, while of 35 other cases not treated with this drug, four died.

The Use of p-Aminobenzenesulfonamide in Type III Pneumococcus Pneumonia. J. H. L. Heintzelman; P. B. Hadley and R. R. Mellon, *Am. J. Med. Sci. 193,* 759 (1937). Nine cases of type III pneumonia were treated orally with Prontylin; seven recovered and two died. Ten similar cases observed during the same period and receiving no special treatment; two recovered and eight died. The mortality for all patients not treated with the drug was 74 per cent., for the treated patients 22 per cent. In some cases the treatment was supplemented by intramuscular injections of Prontosil.

Studies in Chemotherapy. V. Sulphanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice. S. E. Branham and S. M. Rosenthal, *Pub. Health Repts. 52,* 685 (1937). The combined use of Sulfanilamide and serum therapy yielded better results in types I, II and III meningococcic or type I pneumococcic infections in mice than either the sulfonamide or the serum alone. The results suggest that similar combined therapy in man is worthy of trial. The drug was found more effective parenterally than orally.

Experimental Studies With Sulfanilamide and With Prontosil in Hemolytic Streptococcus Infections. R. R. Mellon, P. Gross and F. B. Cooper, *J. A. M. A. 108,* 1858 (1937). Sulfanilamide and Prontosil revealed marked therapeutic effects in mice against hemolytic streptococcus infections. In contrast with results of other authors, favorable therapeutic results were observed with these products in infections with streptococci of medium virulence. Intradermal experimental hemolytic streptococcus infections in guinea pigs subsequently treated with sulfanilamide resulted in the localization and rapid healing which in untreated animals disseminated with fatal results.

The Action of Rubiazol in Various Streptomycoses. Flandin, Poumeau-Delilli, de Graciansky, and Porge, *Bull Soc. Franc. de dermat et syph.* 683, 1936; through *Dermatol. Wochschr. 104,* 624 (1937). The use of *p*-(2′ 4′-diaminophenylazo)-benzenesulfonamide-HCl (Rubiazol) resulted in prompt healing in various erysipeloid diseases.

Treatment of Erysipelas With Prontosil in the Presence of Kidney Ailments. A. Virgil, I. Pascal, and V. Lazarescu, *Klin. Wochschr. 16,* 203 (1937). Two cases of erysipelas of the face were treated with Prontosil. The erysipelas as well as pronounced kidney symptoms which were present were cured.

Strepococcus Meningitis. Report of case with recovery. M. A. Blackstone, *J. Iowa M. Soc. 27,* 255 (1937).

Recovery From Streptococcal Meningitis After Prontosil. M. Frazier, *Brit. Med. J. I,* 1023 (1937). The intravenous injections of a solution of Prontosil S with the oral administration of *p*-aminobenzenesulfonamide resulted in the recovery of a case of streptococcal meningitis.

Chemotherapy of Streptococcal Infections With p-Benzylamino-Benzene-Sulphonamide. B. A. Peters, and R. V. Havard, *Lancet 232,* 1273 (1937). Favorable therapeutic results were obtained with the oral administration of sulfonamide (Proseptasine) in scarlet fever, erysipelas and other streptococcal infections.

ABSTRACTS FROM AND REVIEWS OF THE LITERATURE OF THE SCIENCES SUPPORTING PUBLIC HEALTH

Bacteriology . . . . Louis Gershenfeld, B. Sc., Ph M.
Biochemistry, Nutrition, etc. . . . Arno Viehoever, Ph. D.
Biology . . . . . Marin S. Dunn, Ph. D.
Chemistry . . . . . Arthur Osol, Ph. D.
Pharmacy . . . . . E. Fullerton Cook, Ph. M.
and their assistants

A Study of Methylenedisulfonic Acid and Its Derivatives. J. C. Bauer and G. L. Jenkins. *Jour. Amer. Pharm. Assoc., 26,* 485 (1937). The authors describe attempts to prepare a barbituric acid sulfonal hybrid which would include the hypnophore groups of both compounds. The basic structure of such a hybrid would be $:C.SO_2.NH.CO.NH.SO_2$ and methylenedisulfonic acid, a compound which has been prepared heretofore, would be related to it as malonic acid is related to the barbiturates.

Methylenedisulfonic acid was first prepared by a modification of Schroeter's method yielding larger quantities of a clearer product than obtained by following the original directions. This compound was then converted to methylenedisulfonylchloride, and to alkyl and aryl esters and amides of the acid. Some of these compounds were subsequently used in reactions calculated to produce cyclic ureides of methylenedisulfonic acid, but none of these attempts was successful. However, the authors are still not convinced that such compounds cannot be made. A. O.

Adjustment of pH Value of Procaine Solutions. H. Runeberg. *Farm. Revy., 35,* 757 (1936). Through *Quart. Jour. Pharm. Pharmacol., 10,* 119 (1937). In order to ensure stability, a solution of procaine hydrochloride should have a pH not above 4.3. The normal pH of a solution of the hydrochloride is 5.9; in order to bring the reaction to pH 4.2 it is necessary to add three drops of normal hydrochloric acid to 100 cc. of a 2 or 4 per cent. solution.

A. O.

Decomposition of Methenamine on Sterilization. G. Toni. *Boll. chim.-farm., 76,* 61 (1937). Through *Quart. Jour. Pharm. Pharmacol., 10,* 119 (1937). As there has been some dispute regarding the behavior of solutions of methenamine prepared for injection, experiments were carried out to determine the amount of decomposition which occurred under varied conditions. Solutions of 25 per cent. and 40 per cent. were prepared and put into ampuls; some were not sterilized, some Tyndallized at 60° C., some sterilized for thirty minutes in steam and some in an autoclave at 110° C. for fifteen minutes. After three months the amount of free formaldehyde was determined by Trendelenburg's modification of Jorissen-Vanino's reaction and the pH was determined potentiometrically. The unsterilized 25 per cent. solution showed 0.0688 per cent. of formaldehyde and pH 9.504; the Tyndallized 0.0882 per cent., pH 9.813; the sterilized in steam 0.125 per cent., pH 10.122; the autoclaved 0.115 per cent., pH 10.013. The results with the 40 per cent. solution were similar. The addition of 1 per cent. of hydrolyzed gelatin reduced the decomposition on heating, while with 2 per cent. the sterilized and unsterilized solutions all gave similar figures of about 0.065 per cent. of formaldehyde and pH 8.2. A. O.

The Use of Synthetic Resins in the Preparation of Permanent Bacterial Mounts. B. F. Skiles and C. E. Georgi. *Science, 85,* 367 (1937). The ordinary method of employing Canada balsam as a sealing substance for permanent mounts is quite well known. The authors have tested the usefulness of various synthetic resins in this direction, particularly those whose solutions harden rapidly on exposure to air giving a hard, clear, colorless layer possessing a refractive index very close to that of glass.

In determining the applicability of these resins, bacterial smears were made on glass slides and stained with dyes commonly used, including crystal violet, carbol fuchsin, methylene blue and the Gram stain. Preliminary investigations indicated that butyl acetate, free of acetic acid was the most desirable of the organic solvents used. With one resin ("Pontalite") xylol was substituted for butyl acetate with success. The solutions employed were between 15 and 20 per cent.

Mounts were made in two ways: First, solutions of the synthetic resins were substituted for Canada balsam as the cementing material in the usual manner employing a cover glass. Secondly, a solution of the resin was applied by tilting the glass slide bearing the mount, lengthwise, flooding by means of a dropping pipette and permitting the excess solution to drain off thus leaving a thin, smooth, glass-like film. This may air dry for 30 minutes, or if required at once it may be baked at 135° C. for 5 minutes. No cover slip is used, the thin film of resin serving in its stead. When observing slides so prepared xylol cannot be used to remove the cedar oil due to its solvent action on the resin. The oil may be removed mechanically with lens paper, with ligrom or with gasoline. Mineral oil provides an easier immersion oil to remove. Slides prepared with "Vinylite" (Carbon & Carbon Chem. Corp.) and "Pontalite" (duPont de Nemours & Co.) after one year were still very satisfactory. Solutions of these resins were also used in making permanent mounts of molds. These were impregnated on the surface of a film of the resin which was still slightly sticky, allowed to dry, fixed with mercuric chloride-formaldehyde solution and finally stained. The synthetic resins are considered superior to Canada balsam from the standpoint of ease of manipulation, simplicity, rapidity and cost. L. F. T.

Luminal Injection Solutions. H. Kämpf. *Schweiz. Ap. Ztg., 75,* 261 (1937). Since its introduction by Bayer in 1912 Luminal has grown to great importance in medicine. In the treatment of epilepsy it is employed principally in the form of an injection solution.

The sodium salt has been recommended for preparing such solutions, although solutions already prepared are unstable, a precipitate of phenylethylacetylurea separating. Luminal dissolved in ethyl acetamide has also been employed since the solvent is eliminated unchanged from the body.

Diethylamine seems to provide a means of accomplishing a stable solution. Ampuls were prepared by the following procedure: 10 gm. of Luminal were dissolved in 2.75 gm. of diethylamine and brought to the desired volume with the following mixture: 26 gm. alcohol, 31 gm. glycerin (11.7-13.6 per cent. water) and water to make 100 cc. Since the Luminal in solution is sensitive to heat an aseptic procedure

was used. It is recommended that one test the strength of the diethylamine, since if it be of low content the Luminal dissolves with difficulty.

The diethylamine may be tested by diluting 2 gm., accurately weighed, to 100 cc. with water, 10 cc. of this solution ought, after the addition of dimethylamidobenzol, to require 26.8-27.4 cc. N/10 acid.

The Luminal solution as prepared above should be put into ampuls and sterilized at 60-65° C. on two successive days for a half hour. After three months such ampuls upon examination were found to be unchanged.

In order to simplify the method the solvent mixture was not previously sterilized as before. In this case ampuls containing the Luminal solution were found after several months to contain only 0.8 per cent. carbamid. This small difference in Luminal content would not, however, in practice be important.

In conjunction with this work Schulte (*Pharm. Weekbl., 72,* 1274), reports a somewhat different method. The required amount of alcohol was poured on the Luminal and the diethylamine added. Without heating the solution the glycerin and water are weighed into it. When necessary an aseptic procedure may be carried out in this case also.

Finally, J. J. L. Zwikker (*Pharm. Weekbl., 72,* 1274), prefers a solvent mixture that is used in the production of Luminal ampuls in northern European states—namely, Liquor Barbipheni D. A. K., which possesses the advantage that it contains no basic substances. It directs Phenolbarbital 20 gm., Amylenhydrate 38 gm., Urethane 35 gm., water 7 gm. This forms 100 cc. of liquid. Such a solution may also be prepared with other barbituric acid derivatives. The above solution, although saturated with Luminal, takes up other substances without difficulty, *e. g.,* 5 per cent. of Pyramidon and 2.5 per cent. of Caffeine. One should work under aseptic technic with flasks having vaccine closures. L. F. T.

Mannick's Method for the Determination of Opium. J. R. Nicholls. *The Analyst, 62,* 440 (1937). In the original Mannick method (precipitating as 2:4-dinitrophenol ether) the proportion of fixed alkali to be used is critical and any excess over a certain amount

decreases the sensitivity when applied as a test for small quantities of morphine. The proposed modified method is applicable to morphine salts: Dissolve a weighed quantity of the morphine salt in 30 per cent. ethyl alcohol. To every 100 ml. of solution which must not contain more than 0.1 gm. of morphine salt, add 10 ml. of strong ammonia solution and 5 ml. of a 2 per cent. solution of 1 : 2 : 4-chlorodinitrobenzene in 95 per cent. alcohol. Allow the mixture to stand for 18 hours, filter through a tared Gooch crucible, wash the precipitate with 30 per cent. alcohol and finally with a little ether. Dry the precipitate at 100° C. and weigh. Multiply the weight of the precipitate by 0.632 to obtain anhydrous morphine. This method does not give accurate results with opium since examination of the precipitates shows that they are not pure morphine ether and when tested by Zeisel's method indicate the presence of methoxy groups, which are not present in morphine. W. G. B.

Hypertension Produced With Benzedrine. S. A. Peoples and E. Guttman. *Lancet, Lond., 230,* 1107 (1936). Through *Quart. J. Pharm. & Pharmacol., 10,* 135 (1937). Benzedrine given orally in doses varying from 10 to 80 mg. causes a rise in blood pressure. Its vascular effect is accompanied by psychical effects; a typical change was described by one patient as a feeling of freedom from worry; she felt that the lectures she was listening to were extremely lucid and interesting and an unusual self-confidence was experienced. The objective difference was that the patients became much more talkative; this was specially noteworthy among the depressive patients several of whom talked spontaneously to other people for the first time since admission to the hospital. The authors think that the therapeutic usefulness of benzedrine in mental patients is worth further investigation. L. F. T.

A Comparative Study of Atropine and Syntropan. K. Fromherz. *J. Pharm. & Exper. Therap., 60,* 1 (1937). Atropine as a drug possesses the disadvantage of producing an inhibition in all organs activated by nerves of the autonomic system. In many cases an

effect which is desirable in one organ may become in another an undesirable or even harmful side-action. In consequence of the direct specificity of atropine for the whole parasympathetic system, a more satisfactory therapeutic action than that of atropine can only be expected from a preparation whose action is less specific or whose specificity is somewhat differently directed.

Of many substances tested the tropic ester of 3-diethylamino-2,2-dimethyl-1-propanol was introduced on the basis of clinical experiments in the form of its crystalline acid phosphate under the name of Syntropan. The action of a very closely related substance, namely, an acetyl-tropic ester has already been described (*Arch. f. exper. Path. & Pharmakol., 173,* 86 (1933)), but since Syntropan has more favorable physical properties its comparative action with atropine is presented.

The results in brief show that the relationship between the action of Syntropan and Atropine on various organs is very different. The spasmolytic action of Syntropan particularly on the intestine is comparable with that of atropine while its action on the pupil, on the salivary secretion, and on the vagus is more than 100 to 1000 times less than that of atropine. From this difference in specificity combined with the lower toxicity observed in man and the shorter duration of the action of Syntropan it would seem that this new drug should have many advantages over atropine in therapy. L. F. T.

THE PHILADELPHIA » COLLEGE OF PHARMACY AND SCIENCE » » »

THE ONE HUNDRED AND FIFTEENTH ANNUAL COMMENCEMENT

AT the One Hundred and Fifteenth Annual Commencement of the Philadelphia College of Pharmacy and Science, held there June 9, four men prominent in pharmacy received honorary degrees. They are:

Dr. Frederick Blumenschein, President of the Pennsylvania State Board of Pharmacy and retail pharmacist in Uniontown, Pennsylvania.

Dr. Ralph R. Foran, chief control chemist of Merck and Company, internationally known pharmaceutical and chemical manufacturers in Rahway, New Jersey, and former faculty member at the Philadelphia College.

Dr. Harvey Frank, assistant professor of operative pharmacy at the Philadelphia College.

Dr. Paul N. Leech, world-famed pharmaceutical chemist, who is secretary of the Council on Pharmacy and Chemistry of the American Medical Association in Chicago. Dr. Leech delivered the commencement address to the graduating classes.

In addition to these honorary degrees, seventy-two degrees in course were conferred upon students from many parts of the United States. Degrees this year were granted in bacteriology, biology, chemistry and pharmacy.

One student received the degree of doctor of science in bacteriology. The degree of master of science was conferred upon one student in chemistry, four students in pharmacy, and one student in biology.

Seven students received the degree of bachelor of science in chemistry, six the bachelor of science degree in bacteriology, one the degree of bachelor of science in biology and fifty-one students the degree of bachelor of science in pharmacy.

The following degrees were conferred:

MASTER OF PHARMACY (Honoris Causa)

Frederick Blumenschein, Phar. D.
Ralph Richard Foran, P. D.
Harvey Frank, P. D.
Paul Nicholas Leech, Ph. D.

CANDIDATES FOR DEGREES CONFERRED IN COURSE

DOCTOR OF SCIENCE IN BACTERIOLOGY

Donald Charles Atwood Butts

MASTER OF SCIENCE IN CHEMISTRY

William Henry Hughes

MASTER OF SCIENCE IN PHARMACY

Rudolph DeCerchio
John McCormick Hodges
Peng Wah Lam
Nellie Perry Watts

MASTER OF SCIENCE IN BIOLOGY

Wilton Handley Kimmer

BACHELOR OF SCIENCE IN CHEMISTRY

Harry George Doherty
Abraham Isaac Falkowitz
Alfred Leopold Glass
Clarence Ellwood Hayes, Jr.
Nathan Lionel Reisman
Martin Siris Silverstein
William Mellor Whiteley

BACHELOR OF SCIENCE IN BACTERIOLOGY

Toby Thelma Chertcoff
Rose Franklin
Samuel Kutner
George William Patterson
Gorgonio Pasaje Quimba
Edgar Byers Rodgers

BACHELOR OF SCIENCE IN BIOLOGY

Joseph August Nussle

BACHELOR OF SCIENCE IN PHARMACY

Amy Ketner Adams
LeRoy Morgan Anderson
John Philip Barlement
Mary Vivian Barnisky
Joseph Charles Batchison
Harry Jennings Bomberger, Jr.
Herman Brilliant
Michael Caruso
Harry Joseph Chasanov
Donald Alston Clarke
John Roger Cox
Ira Nathan Dalgarn
Camille Rita DePretore
Mary Isabel Dougherty
Charles Wilson Evans, Jr.
Richard Elfrid Farrow
Max Feldman
Max Fernbach
Joseph Finzimer
Robert Erwin Fish
Enrique Alfredo Gonzales Flores
Charles Henry Giacoponelli
Joseph Thomas Gillen
Louis Goldstein
Reuben Gordon
John Louis Hoffman, 2d
Madeline Oxford Holland
Thomas Bayes Hollis
Jay Paul Hope
Kenneth Ira Karns
Donald Henry Kern
Gilbert Klein

Eugene Leo Kuryloski
Milton Liebowitz
Lucille Mae Long
Albert Francis Morganthaler
Frederick Louis Morganstern, 2d
Peter Samuel Pronko
John Anthony Prudente
Sigmund Rosenberg
Lillian Rubenstone
Roger Michael Russ
Mary Grace Santoflaminio
Isadore Asher Sapolsky
Hymen Shensky
Nicholas Anthony Sigmund
David Louis Spector
Edward King Stanfield
John Kabel Wiley
Wilbur Francis Woelfle
Seldia Zonies

CANDIDATES WHO HAVE COMPLETED SPECIAL COURSES AND HAVE QUALIFIED FOR CERTIFICATES

(This does not include students who completed courses in these subjects for credits for a degree)

Certificates in Bacteriology

Walter Albert Haas
Evan Albert Jones
Duncan Edwin King
Ulysses Thomas Neiffer
Max Stanton Perlstein
Ethel Scheinfeld Portnoff
Sydney Dutch Rosenfeld
Samuel Louis Ross
Fred Anthony Sassi
Helen Magdalena Wachter

Certificates in Clinical Chemistry

Helen Eizabeth Durkin
Rose Gratz
Walter Albert Haas
Evan Albert Jones
Lester Oscar Moore
Ulysses Thomas Neiffer
Max Stanton Perlstein
Ethel Scheinfeld Portnoff
John Gregory Ricketts
Sydney Dutch Rosenfeld
Samuel Louis Ross
George Andrew Stevenson
Helen Magdelena Wachter

AWARD OF PRIZES 1937

GRADUATES IN PHARMACY (Ph. G.)

Designated as "Distinguished"
With General Average Over 90%

Donald Alston Clarke
Max Fernbach
Alfred Leopold Glass
Clarence Ellwood Hayes, Jr.
Martin Siris Silverstein

Designated as "Meritorious"
With General Average Between 85% and 90%

John Philip Barlement
Herman Brilliant
Michael Caruso
Charles Wilson Evans, Jr.
Reuben Gordon
Madeline Oxford Holland
Isadore Asher Sapolsky
David Louis Spector
Harry George Doherty
Abraham Isaac Falkowitz
Nathan Lionel Reisman
Toby Thelma Chertcoff
Rose Franklin

The Procter Prize, a gold medal awarded to the B. Sc. candidate in Pharmacy having the highest average of the class. Earned by:

Max Fernbach

Honorable Mention to

John Philip Barlement
Herman Brilliant
Michael Caruso
Donald Alston Clarke
Charles Wilson Evans, Jr.
Reuben Gordon
Madeline Oxford Holland
Isadore Asher Sapolsky
David Louis Spector

The FRANK GIBBS RYAN PRIZE, a gold medal endowed by the Class of 1884, as a memorial to their distinguished classmate, for the best average in the Chemical and Pharmaceutical Laboratory Courses, is awarded to:

DONALD ALSTON CLARKE

Honorable Mention to

Herman Brilliant — Charles Henry Giacoponelli
Michael Caruso — Madeline Oxford Holland

The WILLIAM B. WEBB MEMORIAL PRIZE, twenty dollars and a bronze medal for the highest average in the branches of Operative Pharmacy, Analytical Chemistry, and Pharmacognosy, is awarded to:

DONALD ALSTON CLARKE

Honorable Mention to

Herman Brilliant — Charles Henry Giacoponelli
Michael Caruso — Madeline Oxford Holland

The FREDERICK WILLIAM HAUSSMANN MEMORIAL PRIZE of one hundred dollars, given to the Pharmacy student with the highest average for the last three years of the course, is awarded to:

DONALD ALSTON CLARKE

Honorable Mention to

Herman Brilliant — Charles Wilson Evans, Jr.
Michael Caruso — Madeline Oxford Holland

A prize of twenty-five dollars offered by THE WOMEN'S AUXILIARY OF THE DAUPHIN COUNTY PHARMACEUTICAL ASSOCIATION to the girl graduating with the highest average:

MADELINE OXFORD HOLLAND

Gold Medals awarded by the Alumni Association to the student of the B. Sc. Class in Pharmacy and to the student of the B. Sc. Class in Chemistry, in Bacteriology, or in Biology who attain the highest scholastic averages, are awarded to:

Bachelor of Science in Pharmacy .....MAX FERNBACH
Bachelor of Science in Chemistry .....MARTIN SIRIS SILVERSTEIN

The REMINGTON MEMORIAL PRIZE, twenty dollars, offered by the Estate of Joseph P. Remington, for the highest average in the examination of Operative Pharmacy and Dispensing, is awarded to:

DONALD ALSTON CLARKE

Honorable Mention to

Albert Francis Morganthaler

The MAHLON N. KLINE THEORETICAL PHARMACY PRIZE, fifty dollars in cash, offered by the Mahlon N. Kline Estate, for the highest average in Theory and Practice of Pharmacy, is awarded to:

DONALD ALSTON CLARKE

Honorable Mention to

Michael Caruso

The ALPHA SIGMA PRIZE is awarded to:

MARTIN SIRIS SILVERSTEIN

Honorable Mention to

Alfred Leopold Glass — Clarence Ellwood Hayes, Jr.

The MAISCH BOTANY PRIZE, a special prize of twenty dollars in gold, offered by Sinclair S. Jacobs of the Class of 1909 to the member of the graduating class who shall have presented the best herbarium collection of plants, or the best thesis on the microscopical structure of medicinal plants, is not awarded this year.

SOLID EXTRACTS

By Ivor Griffith, Ph. M., Sc. D.

Despite the form in which this information is presented it may be accepted as trustworthy and up-to-date. Original sources are not listed but they may be obtained upon request.

"Art thou weary, art thou languid
Art thou sore distressed?"

Such are the words of the fine old hymn, and such, practically were the words recently used, though in a more material or physical sense, to describe the summer ennui of industrial workers, workers in hot factories, who lose a great deal of salt in their perspiration and gain none with the excessive water which they drink. Hence comes a shortage of salt.

Scientific investigators and industrialists are in accord that under hot working conditions the workers labor efficiency is greatly impaired when the body's supply of salt is so decreased, and it is now claimed that it is possible to prevent heat cramps, nausea and muscular fatigue by providing a daily supply of salt greater than that lost in the sweat. The high salt diet necessary for preventing impairment of efficient work can be conveniently and simply obtained through the use of common salt in tablet or in capsule form.

Indeed such tablets (10 grams) are actually sold to the industries, in large amounts, under the name "Heat-beaters".

It is not an easy task ever to draw the line between the intolerance of purists and puritans and the intemperance of fools and pharisees. I quote this silly 1928 tirade against the use of cosmetics and other body adornments. It originates in Guthrie, Oklahoma—out there in the great open spaces where all men are reformers and women have fifteen minutes off on Sunday.

DRESS REFORM PLEDGE!

If averse to signing this, see 2 Corinthians 13: 5.
I promise to abstain from:

Short sleeves—Less than ¾ length
Short skirt—Above the shoe tops
Unnecessarily bright apparel
Attractive head attire
Dressing the hair and the use of Cosmetics.

Just as ridiculous however, when overdone, is the custom, which seemingly is on the increase, whereby young women—kalsomine, lacquer, enamel, veneer, bake, parboil, porcelain finish, shellac and electro-plate their faces with chemicals and corrosives fit only for barns, radiators and board fences.

"Take unto thee sweet spices, stacte and onycha, and galbanum; these sweet spices with pure frankincense; of each shall be a like weight, and thou shalt make it a perfume, a confection after the art of the apothecary, tempered together pure and holy." So runs the command in Exodus.

It will not be sacrilege to aver that Moses must have had nearly as difficult a job converting this formula to perfume as he had changing the stick to a snake. For in the light of present interpretation the formula seems to adapt itself better to a fine spar varnish than to a heavenly scent.

Yet Moses thought so much of it that he restricted its use only to holy purposes—and in an amendment to his decimal decree indicates how incensed he would be were this sacred incense used for private purposes.

"Whosoever shall make like unto that, to smell thereto, shall even be cut off from his people."

Which suggests too that substitution and "something just as good" are not as modern as we thought they were.

Half plant, half animal, such in some respects, is the lowly mushroom. Like other fungi, it has no green coloring matter and can produce no starch. In order to grow it must have available nitrogenous food and available cellulose. It is unlike plants and resembles animals in that it is a high protein source free from starch and during growth consumes oxygen and gives off carbon dioxide.

Comparatively little work has been done on the nutritive value of mushrooms, but they are known to be high in protein, most of it assimilable, and they are also believed to be a fair source of Vitamin B. There are also evidences of the presence of ergosterol and Vitamin D. Principally the mushroom is used as a condimental food and as a table delicacy, often combined with other foods rather than

used alone as an important article of diet. Philadelphia, with its rich history, could hardly be called a mushroom town, yet two-thirds of the country's now tremendous mushroom industry is conducted in the environs of the Quaker City.

For the past decade or so, the term "acidosis" has been used, misused, abused and overused in the business of diagnosis. It afforded a great convenience to the doctor, where a patient with obscure symptoms, insisted upon a high sounding yet definite diagnosis, and the word "acidosis" was bandied about with reckless abandon, and the very available remedy, baking soda, taken internally with neither sense nor safety.

Of course, there *is* the serious condition of acidosis—as every doctor knows.

And recently Dr. Hartmann of Washington has reported a strange palliative for it, namely lactic acid. It was facetiously said that formic acid was the only *ant*-acid. So it was—so it is! But not in the same sense that lactic acid now finds application.

This acid, best known from its occurrence in sour milk and sauerkraut, has proved a "very safe and effective" remedy for severe acidosis, Dr. Hartmann reported.

Mixtures of lactic acid and the related sodium lactate have proved valuable in controlling acidity of the stomach and are of particular value in treating urinary infections in infants and young children.

Dr. Hartmann was discussing a kind of acidosis that is much more severe than the condition that drives the layman to the family medicine chest for a dose of sodium bicarbonate.

Somewhere I saw it reported that a Vermont farmer had been recently penalized to the fullest extent of the law for preserving bottled milk with "preserving powder," more than likely salicylic acid.

That was common practice in the "good old days" of course, when formaldehyde, peroxide, salicylates and any such preservative could be used with impunity. But those were the days before the Food and Drugs Act came along to save the stomachs, not just of bottle fed babes, but of all of us, against such corrosive chemicals.

"To keep milk from turning sour, keep it in the cow," so said the city schoolboy. But much safer for all of us is to let it turn sour rather than load it with vicious chemicals.

Someone has stated that "you can't pin any medals on the Nudists." True, but neither can you—in the idiom, pin any medals on the Prudists, and especially on the men. In one of his lectures, Dr. Sturmer noted that: Feminine dress of today is in far closer harmony with the newer facts pertaining to irradiation as a health measure than is the modern attire of the male. Women have gone far, since Civil War days, in so changing the fashions as to provide for plenty of sun irradiation; and in this span of time the men, alas, have made progress merely to the extent of having shaved off their whiskers, and exposing their chins to the sun. Only on the beach at the seashore does the pipe-smoking sex get an even break when it comes to solar radiation. What should be done about this is a matter far beyond the scope of this discussion. We give it up.

Stand on your head, if you would avoid sunburn seems to be the unpractical message suggested in the following sunburn statistics. The human skin va ies considerably in its tolerance of solar radiation. Light-skinned persons are more sensitive to it than are the dark-skinned, and in most individuals a tolerance may be slowly developed by progressively increasing doses—if one may use the term doses in this connection. Speaking generally, our arms can stand about half again as much as the chest, abdomen or back; the legs a little more than the arms, the backs of our hands about five times as much, and the palms about fifteen times as much, while the foot soles are most resistive, because here the skin is thickest, and the outer skin is a poor conductor of radiation. But persons who do not tan must be very careful in taking sun baths.